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Vitamin E and Disease Risk: Research Focus Turns on Genetic Polymorphisms and Molecular Mechanisms

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A possible preventive effect of supplementation with vitamin E (α-tocopherol) against atherosclerosis and other diseases such as cancer and neurodegeneration has been addressed in many studies (reviewed in [1-3]). Whereas in most animal studies vitamin E supplementation reduces cardiovascular disease (CVD), human randomized clinical trials and epidemiologic studies have reported both positive and negative outcomes (reviewed in [2]). Meta-analyses of the clinical studies even suggested an increased all-cause mortality with high doses of vitamin E supplementation [4,5], although other more recent studies did not confirm this [6,7]. Similar to that, a significant increase in prostate cancer risk was observed in the recent follow-up study of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [8], whereas a preventive effect of vitamin E was observed in a study on nonalcoholic steatohepatitis (NASH) in adults without diabetes [9]. Intriguingly, based on the molecular properties of vitamin E as free radical scavenger, some of these results were not expected, suggesting that the current molecular models of vitamin E action may need to be revised.

Several factors have been proposed to explain the often mixed outcome of vitamin E supplementation, such as the relatively short duration of supplementation, the low dose used unable to prevent free radicals, the presence of high baseline levels of vitamin E already present in the normal diet sufficient to prevent disease symptoms, and a number of other reasons [10,11]. Moreover, the potential health effects of vitamin E supplementation may become evident only when combined with vitamin C (L-ascorbic acid) and other dietary phytochemicals and micronutrients (e.g. selenium), or under specific environmental and patho-physiological circumstances with assumed local depletion of vitamin E by oxidants associated with inflammation, infection, smoking or UV irradiation.

Genetic and epigenetic polymorphisms in genes involved in vitamin E uptake, distribution, metabolism and molecular action may be a further important factor determining the protective effects of vitamin E, and explain the different response of patients to supplemented vitamin E (discussed in [12-14]). Whereas for many gene polymorphisms a link to an altered disease risk decreased by vitamin E still needs to be established, the rapid growth of genomics information and insight into vitamin E responsive gene function is expected to accelerate discoveries in this research field.

For long, the focus of vitamin E research has been to relate a specific disease risk with the plasma levels of vitamin E, in part controlled by polymorphisms within vitamin E transport genes. So far, individual differences in vitamin E plasma levels have been linked with polymorphisms in several genes, such as the haptoglobin gene [15], α-TTP and hTAP1/SEC14L2 [16], CD36 [17], and a number of other genes [13,18-21]. However, as outlined in the following, with more and more insight into genes regulating the intracellular transport and molecular action of vitamin E, additional genetic polymorphisms may gain importance.

In view of the recently observed higher [8], and, in the presence of certain polymorphisms [16], lower prostate cancer risk after vitamin E supplementation, it is conceivable that some polymorphisms may contribute not only to the beneficial but also to the adverse effects. Moreover, some gene polymorphisms may not only influence the plasma concentration, but also the cellular regulatory function of vitamin E in tissues. In support for this, polymorphisms detected in genes regulated by vitamin E, such as CD36 [17,22-26] or cytokines [27] may render them more (or less) responsive to the effects of vitamin E supplementation.

Thus, specific gene polymorphisms may correlate with the disease risk by affecting the expression level and activity of genes in peripheral tissues as a consequence of altered local levels and molecular actions of vitamin E, whereas the plasma vitamin E levels may be secondary. In this respect, the observed changes in prostate cancer risk associated with higher or lower plasma vitamin E levels may more reflect the altered molecular action of vitamin E in tissues resulting from polymorphisms in genes like hTAP1/2/3, α-TTP, CD36 and others [13,16,17,22,28-30].

Vitamin E supplementation may modulate hTAP1-regulated events such as cell proliferation or secretion within prostate or breast cancer cells by regulating signaling and gene expression (e.g. via phosphatidylinositol-kinases), or by influencing the biosynthesis of cholesterol/steroids (e.g. via influencing cholesterol/steroid biosynthesis by regulating squalene epoxidase or HMG-CoA reductase) [29-33]. It is interesting to note that for these activities of vitamin E in tissues, the other natural tocopherol analogues (α-, β-, γ-, δ-tocopherols and tocotrienols, α -tocopheryl quinone, α -tocopheryl phosphate) may also play a role, that may be worth considering in future studies [32,34]. Whether hTAP proteins also influence the disease risk by modulating the biosynthesis of α -tocopheryl phosphate, and consequent PI3K/Akt/VEGF and angiogenesis is currently under investigation in our laboratory [35,36].

More basic research into the molecular and cellular function of the vitamin E regulatory genes is required to establish firm associations between specific gene polymorphisms, vitamin E, and disease risk. The Journal "*Vitamins & Trace Elements*" promises rapid peer-reviewed publication dedicated to this type of research. Online publication may facilitate the establishment of hyperlinks documenting gene function in relation with genomics data often assembled only in silico. Future developments within The Open Access initiative may accelerate

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innovations and discoveries by bridging the gap between genomics information and more descriptive functional gene data.

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